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## **CCDC26, CDKN2BAS, RTEL1 and TERT Polymorphisms in pediatric brain tumor susceptibility**

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**Abstract:** The role of genetic polymorphisms in pediatric brain tumor (PBT) etiology is poorly understood. We hypothesized that single nucleotide polymorphisms (SNPs) identified in genome-wide association studies (GWAS) on adult glioma would also be associated with PBT risk. The study is based on the Cefalo study, a population-based multicenter case-control study. Saliva DNA from 245 cases and 489 controls, aged 7-19 years at diagnosis/reference date, was extracted and genotyped for 29 SNPs reported by GWAS to be significantly associated with risk of adult glioma. Data were analyzed using unconditional logistic regression. Stratified analyses were performed for two histological subtypes: astrocytoma alone and the other tumor types combined. The results indicated that four SNPs, CDKN2BAS rs4977756 ( $p = 0.036$ ), rs1412829 ( $p = 0.037$ ), rs2157719 ( $p = 0.018$ ) and rs1063192 ( $p = 0.021$ ), were associated with an increased susceptibility to PBTs, whereas the TERT rs2736100 was associated with a decreased risk ( $p = 0.018$ ). Moreover, the stratified analyses showed a decreased risk of astrocytoma associated with RTEL1 rs6089953, rs6010620 and rs2297440 ( $p$  trend = 0.022,  $p$  trend = 0.042,  $p$  trend = 0.029, respectively) as well as an increased risk of this subtype associated with RTEL1 rs4809324 ( $p$  trend = 0.033). In addition, SNPs rs10464870 and rs891835 in CCDC26 were associated with an increased risk of non-astrocytoma tumor subtypes ( $p$  trend = 0.009,  $p$  trend = 0.007, respectively). Our findings indicate that SNPs in CDKN2BAS, TERT, RTEL1 and CCDC26 may be associated with the risk of PBTs. Therefore, we suggest that pediatric and adult brain tumors might share common genetic risk factors and similar etiological pathways.

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## ***CCDC26, CDKN2BAS, RTEL1, and TERT Polymorphisms in Pediatric Brain Tumor Susceptibility***

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**Abstract**

The role of genetic polymorphisms in pediatric brain tumor (PBT) etiology is poorly understood. We hypothesized that single nucleotide polymorphisms (SNPs) identified in genome-wide association studies (GWAS) on adult glioma would also be associated with PBT risk. The study is based on the Cefalo study, a population-based multicenter case-control study. Saliva DNA from 245 cases and 489 controls, aged 7-19 years at diagnosis/reference date, was extracted and genotyped for 29 SNPs reported by GWAS to be significantly associated with risk of adult glioma. Data were analyzed using unconditional logistic regression. Stratified analyses were performed for two histological subtypes: astrocytoma alone and the other tumor types combined. The results indicated that four SNPs, *CDKN2BAS* rs4977756 ( $p=0.036$ ), rs1412829 ( $p=0.037$ ), rs2157719 ( $p=0.018$ ), and rs1063192 ( $p=0.021$ ), were associated with an increased susceptibility to PBTs, whereas the *TERT* rs2736100 was associated with a decreased risk ( $p=0.018$ ). Moreover, the stratified analyses showed a decreased risk of astrocytoma associated with *RTEL1* rs6089953, rs6010620, and rs2297440 ( $p_{\text{trend}}=0.022$ ,  $p_{\text{trend}}=0.042$ ,  $p_{\text{trend}}=0.029$ , respectively) as well as an increased risk of this subtype associated with *RTEL1* rs4809324 ( $p_{\text{trend}}=0.033$ ). In addition, SNPs rs10464870 and rs891835 in *CCDC26* were associated with an increased risk of non-astrocytoma tumor subtypes ( $p_{\text{trend}}=0.009$ ,  $p_{\text{trend}}=0.007$ , respectively). Our findings indicate that SNPs in *CDKN2BAS*, *TERT*, *RTEL1*, and *CCDC26* may be associated with the risk of PBTs. Therefore, we suggest that pediatric and adult brain tumors might share common genetic risk factors and similar etiological pathways.

## Summary

The role of genetic polymorphisms in pediatric brain tumor (PBT) etiology is poorly understood. In this study, we tested the hypothesis that single nucleotide polymorphisms identified by genome-wide association studies on adult glioma are also associated with PBT risk.

## Introduction

Brain tumors are the second most common type of pediatric cancer and the leading cause of childhood cancer mortality. The etiology of pediatric brain tumors (PBTs) is poorly understood (1). As in adults (2), the only established risk factors for brain tumors in children are exposure to high doses of ionizing radiation and several inherited disorders, and these cause only a minority of cases. Therefore, it is likely that brain tumorigenesis results from complex interactions between genetic and epigenetic variations in concert with exposure to environmental factors (1).

Although large genetic studies on adult brain tumors have been conducted (3-7), very few and only small studies of brain tumors in children and adolescents have been reported (8-11). In the last few years, four genome-wide association studies (GWAS) on adult glioma identified seven susceptibility loci at 5p15.33 (*TERT*), 8q24.21 (*CCDC26*), 9p21.3 (*CDKN2A-CDKN2B*), 20q13.33(*RTEL1*), 11q23.3 (*PHLDB1*), and 7p11.2 (*EGFR*) (4-7). However, limited data are available on the role of genetic polymorphisms in the etiology of PBTs, probably because of difficulties in collecting a sufficient number of DNA samples. Considering this lack of knowledge about genetic risk factors for brain tumors in children, it is important to identify germ-line DNA polymorphisms that might influence the susceptibility to PBTs.

The aim of this study, based on the largest series of PBT cases to date, was to test the hypothesis that the single nucleotide polymorphisms (SNPs) identified by GWAS on adult glioma are also associated with the risk of brain tumors in children.

## **Materials and methods**

### **Study population and procedures**

This study is based on the Cefalo study, a large, international, population-based, case-control study of brain tumors in children and adolescents conducted in centers in Sweden, Denmark, Norway, and Switzerland. All centers followed a common protocol for data collection, as described in more detail elsewhere (12,13). Eligible cases were children aged 7-19 years during the period 1 April 2004 to 31 August 2008, diagnosed with a primary intracranial brain tumor defined according to the International Classification of Childhood Cancer, third edition (ICCC-3) (14), group III, restricted to ICD-O-3 location C71 and subclassified according to the fourth edition of the [World Health Organization](#) (WHO) classification of tumors of the central nervous system (15). Medulloblastoma cases will be the subject of a separate study, and therefore have been excluded from the present analysis. Two controls per case were randomly selected from the general population matched to the case by age, sex, and geographical region. Interviews were conducted with 352 (82%) cases and 646 (71%) controls. Participants with neurofibromatosis or tuberous sclerosis were excluded from the analyses. The study was approved by the national data protection boards and ethical committees in all participating countries, and written informed consent was obtained from all participants and/or their parents.

The Oragene self-collection kit (DNA Genotek, Ottawa, ON, Canada) was used for saliva collection and DNA extraction, following the manufacturer's recommended protocol. DNA samples are stored at the Karolinska Institutet Biobank. The DNA yield was quantitated by

using PicoGreen (Invitrogen, Carlsbad, CA, USA). Overall, saliva DNA from 245 cases and 489 controls was included in this study.

### **SNP selection and genotyping**

A total of 29 SNPs reported by GWAS to be significantly associated with risk of adult glioma were selected for genotyping (4-7). Genotyping was performed at the Mutation Analysis core Facility (MAF), Clinical Research Centre, Huddinge University Hospital, Stockholm, Sweden, with staff blinded to sample status, using the SequenomPlex Gold platform with matrix-assisted laser desorption/ionization-time-of-flight (MALDI-TOF) mass spectrometry. The average success rate was 97% and the concordance rate for duplicate genotyping was 100%.

### **Statistical analysis**

The consistency of allele frequencies with Hardy-Weinberg equilibrium (HWE) was assessed in the controls for all SNPs using the  $\chi^2$  goodness-of-fit test, and  $p < 0.001$  was considered statistically significant. Analyses were performed based on the subset of Cefalo subjects who provided saliva sample. Unconditional logistic regression was used to estimate the association between SNPs and PBT susceptibility based on the Cochran–Armitage trend test of additivity (trend) as well as dominant (DOM) and recessive (REC) models, with adjustment for the matching variables (age, sex, and country). The allelic frequencies of the genotyped SNPs were compared between cases and controls using the  $\chi^2$  test. Analyses were also conducted stratified by astrocytoma alone and the combination of other tumor types, including ependymoma, intracranial embryonal tumors (except medulloblastoma), other gliomas, other specified intracranial neoplasms, and unspecified intracranial neoplasms. Country specific analyses were performed to assess consistency across countries. The Wald test was used to evaluate the significance of interactions between SNPs and demographic variables and  $D'$ , a

measure of the linkage disequilibrium (LD) between the genotyped SNPs, was calculated. Haploblocks were defined based on the default LD block parameters in Haploview v4.2. Haplotype analyses were performed for the haplotype blocks harboring the SNPs that were found to be associated with PBTs. Haplotypes with a frequency of >1% were considered in the analyses. The effects of specific haplotypes were analyzed if the distribution of all the haplotypes was suggestively different between cases and controls ( $p < 0.05$  for all PBTs;  $p < 0.1$  for subgroup analyses). Selection of SNPs for the analyses was based on a priori knowledge from GWAS on adults, and therefore odds ratios (ORs) are presented with 95% confidence intervals (CIs). The possibility of false-positive findings was, however, considered by also providing the reference  $p$  value for an experiment-wide significance with Bonferroni correction. The analyses were performed using PLINK v1.07 (16) and SAS statistical software version 9.3 (SAS Institute, Inc., Cary, NC, USA).

## Results

We successfully genotyped 29 SNPs in 245 cases and 489 controls. The distributions of allele frequencies in the controls were in agreement with the Hardy-Weinberg equilibrium. Table 1 shows demographic characteristics of cases and controls, and the distributions of diagnostic subtypes. The age and sex distributions were similar in cases and controls. More than 50% of cases were diagnosed with astrocytoma. No significant interactions were detected between SNPs and confounders including age, sex and country (Table 2).

As shown in Table 2, *TERT* rs2736100 A allele was associated with a decreased risk of PBTs ( $OR_{DOM}$  0.66 [95% CI 0.46-0.93],  $p=0.018$ ), whereas the SNPs rs4977756 G allele ( $OR_{DOM}$  1.45 [95% CI 1.03-2.06],  $p=0.036$ ), rs1412829 G allele ( $OR_{DOM}$  1.45 [95% CI 1.02-2.05],  $p=0.037$ ), rs2157719 C allele ( $OR_{DOM}$  1.53 [95% CI 1.08-2.19],  $p=0.018$ ), and rs1063192 G



allele ( $OR_{DOM}$  1.53 [95% CI 1.07-2.19],  $p=0.021$ ) in *CDKN2BAS* were associated with increased susceptibility to this tumors.

The stratified analyses of two histological subtypes indicated that the risk effects of *CDKN2BAS* rs1063192, rs2157719, rs1412829, and rs4977756 remained significant in patients with astrocytoma ( $p_{trend}=0.036$ ,  $p_{trend}=0.034$ ,  $p_{trend}=0.044$ , and  $p_{trend}=0.023$ , respectively), whereas the protective effect of *TERT* rs2736100 was more evident in patients with other brain tumor subtypes ( $OR_{DOM}$  0.53 [95% CI 0.34-0.85],  $p=0.007$ ). Moreover, the stratified analyses showed a decreased risk of astrocytoma associated with the polymorphisms *RTEL1* rs6089953 A allele, rs6010620 A allele, and rs2297440 T allele ( $p_{trend}=0.022$ ,  $p_{trend}=0.042$ , and  $p_{trend}=0.029$ , respectively), as well as an increased risk of this subtype associated with the C allele of *RTEL1* rs4809324 ( $p_{trend}=0.033$ ). In addition, an increased risk of non-astrocytoma tumor subtypes was associated with the SNPs rs10464870 C allele and rs891835 G allele in *CCDC26* ( $p_{trend}=0.009$  and  $p_{trend}=0.007$ , respectively) (Table 3).

The non-significant findings, possibly resulting from the limited statistical power of the study, are shown in the online appendix Tables S1-S3 and the raw data showing the number of cases and controls for each genotype of significant SNPs are reported in Table S4.

Strong LD ( $D' \geq 0.95$ ) was observed between three of the genotyped SNPs in *CDKN2BAS* (rs1412829, rs2157719, and rs1063192), and four SNPs in *RTEL1* (rs6089953, rs6010620, rs2297440, and rs4809324). For each of the two blocks, three haplotypes with frequency of  $>1\%$  were found. The distribution of haplotypes was different for PBT patients compared to controls for the *CDKN2BAS* block ( $\chi^2=7.0$ ,  $df=2$ ,  $p=0.030$ ) and showed a tendency to be different for the *RTEL1* block ( $\chi^2=5.9$ ,  $df=2$ ,  $p=0.053$ ). The most common haplotype (ATA) of *CDKN2BAS* SNPs had a significant protective effect compared with the other haplotypes combined ( $OR$  0.75 [95% CI 0.60-0.93],  $p=0.009$ ) whereas the second most common

haplotype (GCG) had a significant risk effect (OR 1.32 [95% CI 1.06-1.64],  $p=0.012$ ). The haplotype analyses suggested an increased risk of PBTs by increasing the number of risk alleles in *CDKN2BAS* and *RTEL1* SNPs. In the astrocytoma subgroup, the same haploblocks and haplotypes with frequencies of  $>1\%$  were detected. However, in this subgroup, the distribution of haplotypes in the *RTEL1* block was significantly different between patients and controls ( $\chi^2=9.0$ ,  $df=2$ ,  $p=0.011$ ) while this difference was not statistically significant in the *CDKN2BAS* block ( $\chi^2=5.7$ ,  $df=2$ ,  $p=0.059$ ). In the astrocytoma subgroup, a significant protective effect was observed for the most common haplotype (ATA) of *CDKN2BAS* SNPs compared with the other haplotypes combined (OR 0.73 [95% CI 0.56-0.95],  $p=0.021$ ) whereas the second most common haplotype (GCG) showed a significant risk effect (OR 1.34 [95% CI 1.02-1.76],  $p=0.036$ ). Moreover, in the *RTEL1* block, the second most common haplotype (AATT) had a significant protective effect compared with the other haplotypes combined (OR 0.67 [95% CI 0.47-0.95],  $p=0.023$ ) whereas the third most common haplotype (GGCC) had a significant risk effect (OR 1.57 [95% CI 1.06-2.34],  $p=0.026$ ) (Table 4).

Overall, we performed 116 testing procedures as described above. When the Bonferroni correction is applied, the reference  $p$  value is 0.0004 for an experiment-wide significance level of 0.05, and 0.0009 for a significance level of 0.10; none of the observed associations met these limits. The consistency of results across countries was investigated and the results of stratified analyses are reported in the online appendix Tables S5-S8. No significant differences between countries were observed. **Discussion**

The results of this study indicate that several SNPs associated with adult glioma risk are also associated with the risk of PBTs. Our findings suggest that SNPs rs4977756 G allele, rs1412829 G allele, rs2157719 C allele, and rs1063192 G allele in *CDKN2BAS* may increase the risk of PBTs, whereas the A allele of *TERT* rs2736100 polymorphism may confer protection against PBTs. In addition, polymorphisms rs6089953 A allele, rs6010620 A allele,

and rs2297440 T allele in *RTEL1* were associated with decreased susceptibility to astrocytoma, whereas the C allele of *RTEL1* rs4809324 was associated with an increased risk of this subtype. Furthermore, an increased risk of non-astrocytoma tumor subtypes associated with polymorphisms *CCDC26* rs10464870 C allele and rs891835 G allele was detected. Our findings suggest that genetic risk profiles of PBTs differ by histology.

To our knowledge, this study represents the largest series of pediatric brain tumor cases assembled for genetic association testing to date. The association between the 29 SNPs investigated in this study and the risk of PBTs has not been examined in previous studies (8-11). The SNPs were selected a priori for analyses in this study based on findings in GWAS on adult glioma, and our significant findings of associations between SNPs in *CDKN2BAS*, *TERT*, *RTEL1*, and *CCDC26* and risk of PBTs were consistent with findings on adult brain tumors with respect to the direction of ORs for the minor alleles (4-7).

*CDKN2BAS* (*ANRIL*) encodes antisense non-coding RNA in the *INK4* locus which is a long non-coding RNA (ncRNA). The exact function of *CDKN2BAS* is unclear, but it is known to be involved in regulating the expression of *CDKN2A* and *CDKN2B* genes that encode cyclin-dependent kinase inhibitors and block cell cycle division during the G1/S phase. Therefore, *CDKN2BAS* has a regulatory role in the context of cellular proliferation, and its alterations result in abnormal self-renewing capabilities typical of cancer cells (17,18). Germ-line mutations in *CDKN2BAS* predispose to a wide variety of human cancers (19,20).

[ENREF 17](#) [ENREF 4](#)

Telomerase reverse transcriptase (TERT) is a catalytic subunit of telomerase that maintains telomere by adding telomeric repeat sequences onto chromosome ends. Telomerase expression can prevent telomere erosion in most eukaryotic cells, and cancer cells can prevent telomere loss through the abnormal upregulation of telomerase (21). [ENREF 18](#) The mutant

allele of *TERT* rs2736100, which is an intronic polymorphism, may downregulate telomerase expression and consequently decrease the risk of brain tumors.

*RTEL1* produces regulator of telomere elongation helicase 1 which is essential for telomere maintenance and genome stability by preventing homologous recombination (22). Polymorphisms in *RTEL1* are correlated with high grade glioma in adults (4,5,7,23). [ENREF 4](#) In contrast, *CCDC26* variations are associated with low grade tumors (4,5,23). *CCDC26* encodes a retinoic acid-dependent regulator of cell differentiation and death. *CCDC26* increases apoptosis induced by death stimuli in neuroblastoma cells (24) and in glioblastoma cells with downregulation of telomerase activity (25).

The majority of genetic variations found in this study to be associated with the risk of PBTs are related to telomerase activity which has an important role in the initiation and progression of gliomas (26). Moreover, it has been shown that telomerase expression is related to high grade gliomas and poor survival (27,28). Thus, telomerase could be considered as a therapeutic target for brain tumors (29,30).

The aim of this study was to provide evidence of the associations between SNPs and PBT risk, and not to investigate the mechanisms behind such associations; nevertheless the fact that we did not consider the effect of environmental risk factors represents a limitation of this work. Therefore, additional studies are needed to examine potentially relevant gene-environment interactions and to explore the mechanisms through which these genetic polymorphisms influence cancer susceptibility.

The present study was conducted based on a specific hypothesis that may lead to detection of clinically meaningful risk and protective factors. Moreover, the selection of SNPs for analysis was based on a priori knowledge from GWAS on adults, and therefore Bonferroni correction may be overly conservative and may make researchers miss important findings (31). To be

able to evaluate potential false-positive findings, reference p values with Bonferroni corrections have been presented and the consistency of results across four countries has been reported. No significant differences between countries were observed. Replication studies are necessary to confirm these results in larger sample sizes.

In conclusion, the present findings indicate that SNPs in *CDKN2BAS* are associated with increased susceptibility to PBTs, whereas *TERT* polymorphisms may decrease the risk of these tumors. Moreover, polymorphisms in *RTEL1* and *CCDC26* genes are associated with the risk of astrocytoma and non-astrocytoma subtypes, respectively. Thus, we suggest that pediatric and adult brain tumors might share common genetic risk factors and similar etiological pathways.

### **Supplementary material**

Supplementary Tables S1-S3 can be found at <http://carcin.oxfordjournals.org/>.

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### **Conflict of Interest Statement**

None declared.

### **URLs**

PLINK: <http://pngu.mgh.harvard.edu/~purcell/plink/>

SAS: <http://www.sas.com/>

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**Table 1. Characteristics of cases and controls**

Characteristics	Cases	Controls
No. of participants	245	489

<b>Sex</b>		
Males	136 (56%)	261 (53%)
Females	109 (44%)	228 (47%)
<b>Age-group (at reference date)</b>		
7-9 years old	48 (20%)	112 (23%)
10-14 years old	108 (44%)	219 (45%)
15-19 years old	89 (36%)	158 (32%)
<b>Country</b>		
Sweden	106 (43%)	174 (36%)
Norway	24 (10%)	62 (13%)
Denmark	62 (25%)	134 (27%)
Switzerland	53 (22%)	119(24%)
<b>Type of tumor (ICCC-3 group III)<sup>a</sup></b>		
Astrocytoma (IIIb)	134 (55%)	
Pilocyticastrocytoma	93	
Supependymalgiant cell astrocytoma	5	
Pleomorphicxanthoastrocytoma	4	
Diffuse astrocytoma	13	
Anaplastic astrocytoma	11	
Fibrillaryastrocytoma	2	
Glioblastoma	5	
Giant cell glioblastoma	1	
Other gliomas (IIIId)	20 (8%)	
Malignantglioma	11	
Oligoastrocytoma	2	
Oligodendroglioma	6	
Anaplastic oligodendroglioma	1	
Ependymoma (IIIa)	19 (8%)	
Subependymoma	2	
Choroidplexuspapilloma	4	
Choroidplexuscarcinoma	1	
Ependymoma	7	
Papillaryependymoma	1	
Anaplastic ependymoma	4	
Intracranial embryonal tumors (IIIc)	7 (3%)	
CNS primitive neuroectodermaltumor	6	
Neuroepithelioma	1	
Other specified intracranial neoplasms (IIIe)	49 (20%)	

Germinoma	7
Yolksactumor	1
Teratoma, mature	1
Haemangioblastoma	1
Desmoplastic infantile ganglioglioma	2
Dysembryoplastic neuroepithelialtumor	6
Ganglioglioma	26
Anaplasticganglioglioma	1
Centrolneurocytoma	3
Neurilemoma	1
Unspecified intracranial neoplasm (III f)	16 (6%)

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a: Restricted to ICD-O-3 location C71, subclassified according to WHO histological

subclassification, 2007; patients with neurofibromatosis and tuberous sclerosis were excluded.

**Table 2. Summary results for SNPs associated with pediatric brain tumors**

SNP	Chr.	Gene	Location (bp)	Minor allele	MAF <sup>a</sup> in cases	MAF <sup>a</sup> in controls	Model	OR <sup>b</sup>	95% CI	P	CHISQ	Pinteraction <sup>c</sup>
rs2736100	5	<i>TERT</i>	1286516	A	0.47	0.50	Dominant	0.66	0.46-0.93	0.018		0.702
							Recessive	1.19	0.82-1.71	0.359		
							Additive	0.89	0.72-1.12	0.351		
							Allelic			0.333	0.94	
rs1063192	9	<i>CDKN2BAS</i> <i>CDKN2B</i>	22003367	G	0.52	0.45	Dominant	1.53	1.07-2.19	0.021		0.889
							Recessive	1.36	0.95-1.95	0.095		
							Additive	1.31	1.05-1.63	0.015		
							Allelic			0.009	6.64	
rs2157719	9	<i>CDKN2BAS</i>	22033366	C	0.51	0.44	Dominant	1.53	1.08-2.19	0.018		0.825
							Recessive	1.36	0.94-1.97	0.099		
							Additive	1.32	1.06-1.64	0.014		
							Allelic			0.009	6.67	
rs1412829	9	<i>CDKN2BAS</i>	22043926	G	0.50	0.43	Dominant	1.45	1.02-2.05	0.037		0.734
							Recessive	1.38	0.95-1.99	0.089		
							Additive	1.29	1.04-1.61	0.021		
							Allelic			0.014	6.04	
rs4977756	9	<i>CDKN2BAS</i>	22068652	G	0.49	0.42	Dominant	1.45	1.03-2.06	0.036		0.954
							Recessive	1.30	0.89-1.91	0.176		
							Additive	1.27	1.02-1.59	0.032		
							Allelic			0.024	5.09	

**a:** MAF=Minor Allele Frequency      **b:** ORadjusted for age, sex, and country **c:** P value for interactions between SNPs and demographic variables including age, sex and country

**Table 3. Summary results for SNPs associated with pediatric brain tumors stratified by histological subtypes**

SNP	Chr.	Gene	Location (bp)	Minor allele	MAF <sup>a</sup> in cases	MAF <sup>a</sup> in controls	Model	OR <sup>b</sup>	95% CI	P	CHISQ
<b>Astrocytoma</b>											
rs1063192	9	<i>CDKN2BAS</i> <i>CDKN2B</i>	22003367	G	0.52	0.45	Dominant	1.84	1.15-2.94	0.011	4.29
							Recessive	1.21	0.76-1.91	0.419	
							Additive	1.34	1.02-1.76	0.036	
							Allelic			0.038	
rs2157719	9	<i>CDKN2BAS</i>	22033366	C	0.51	0.44	Dominant	1.75	1.11-2.77	0.016	4.43
							Recessive	1.26	0.79-1.99	0.329	
							Additive	1.34	1.02-1.76	0.034	
							Allelic			0.035	
rs1412829	9	<i>CDKN2BAS</i>	22043926	G	0.50	0.43	Dominant	1.64	1.05-2.57	0.029	4.09
							Recessive	1.28	0.81-2.03	0.294	
							Additive	1.32	1.01-1.74	0.044	
							Allelic			0.043	
rs4977756	9	<i>CDKN2BAS</i>	22068652	G	0.5	0.42	Dominant	1.85	1.17-2.91	0.008	

rs6089953	20	<i>RTEL1</i>	62291008	A	0.18	0.25	Recessive	1.25	0.78-2.01	0.358	5.02
							Additive	1.38	1.05-1.82	0.023	
							Allelic			0.025	
							Dominant	0.64	0.43-0.96	0.032	
rs6010620	20	<i>RTEL1</i>	62309839	A	0.19	0.25	Recessive	0.49	0.19-1.31	0.157	5.46
							Additive	0.67	0.48-0.95	0.022	
							Allelic			0.019	
							Dominant	0.66	0.44-0.99	0.048	
rs2297440	20	<i>RTEL1</i>	62312299	T	0.17	0.24	Recessive	0.59	0.24-1.45	0.254	4.27
							Additive	0.71	0.50-0.99	0.042	
							Allelic			0.039	
							Dominant	0.64	0.41-0.98	0.038	
rs4809324	20	<i>RTEL1</i>	62318220	C	0.15	0.10	Recessive	0.52	0.19-1.37	0.187	5.18
							Additive	0.68	0.47-0.96	0.029	
							Allelic			0.023	
							Dominant	1.54	0.98-2.39	0.060	
							Recessive	2.94	0.78-11.14	0.112	

							Additive	1.54	1.04-2.28	0.033	
							Allelic			0.029	4.74
<b>Other</b>											
rs2736100	5	<i>TERT</i>	1286516	A	0.44	0.50	Dominant	0.54	0.34-0.85	0.007	
							Recessive	1.07	0.64-1.77	0.802	
							Additive	0.78	0.57-1.07	0.122	
							Allelic			0.139	2.19
rs10464870	8	<i>CCDC26</i>	130477823	C	0.32	0.23	Dominant	1.70	1.11-2.60	0.014	
							Recessive	1.78	0.87-3.66	0.115	
							Additive	1.53	1.11-2.11	0.009	
							Allelic			0.004	8.11
rs891835	8	<i>CCDC26</i>	130491752	G	0.34	0.24	Dominant	1.59	1.04-2.44	0.032	
							Recessive	2.32	1.18-4.57	0.015	
							Additive	1.55	1.13-2.14	0.007	
							Allelic			0.003	8.65

**a:** MAF=Minor Allele Frequency

**b:** ORadjusted for age, sex, and country



**Table 4. Haplotype analysis of SNPs in *CDKN2BAS* and *RTEL1***

SNPs	Haplotype	Frequency	OR <sup>a</sup>	95% CI	P
<i>CDKN2BAS</i> : rs1412829, rs2157719, rs1063192	ATA	0.52	0.75	0.60-0.93	0.009
	GCG	0.45	1.32	1.06-1.64	0.012
	ATG	0.02	0.89	0.56-1.43	0.814
<i>RTEL1</i> : rs6089953, rs6010620, rs2297440, rs4809324	GGCT	0.65	1.03	0.81-1.32	0.787
	AATT	0.23	0.79	0.61-1.02	0.074
	GGCC	0.11	1.39	0.99-1.95	0.055
<b>Astrocytoma</b>					
<i>CDKN2BAS</i> : rs1412829, rs2157719, rs1063192	ATA	0.53	0.73	0.56-0.95	0.021
	GCG	0.44	1.34	1.02-1.76	0.036
	ATG	0.02	0.79	0.21-2.94	0.725
<i>RTEL1</i> : rs6089953, rs6010620, rs2297440, rs4809324	GGCT	0.65	1.06	0.81-1.39	0.676
	AATT	0.23	0.67	0.47-0.95	0.023
	GGCC	0.11	1.57	1.06-2.34	0.026

**a:** Odds ratio for haplotype compared with all other haplotypes adjusted for age, sex, and country

**Table S1. Summary results for SNPs unassociated with pediatric brain tumors**

SNP	Chr.	Location (bp)	Minor allele	MAF <sup>ψ</sup> in cases	MAF <sup>ψ</sup> in controls	Model	OR <sup>£</sup>	95% CI	P	CHISQ
rs7530361	1	100462860	C	0.144	0.1656	Dominant	0.7977	0.5631-1.13	0.2032	1.129
						Recessive	0.9425	0.347-2.56	0.9075	
						Additive	0.8339	0.6127-1.135	0.2479	
						Allelic			0.2881	
rs501700	1	100520311	A	0.148	0.1607	Dominant	0.861	0.5991-1.238	0.4188	0.3657
						Recessive	0.9696	0.3565-2.637	0.9518	
						Additive	0.8895	0.6477-1.222	0.4693	
						Allelic			0.5454	
rs2072532	2	40366301	G	0.4604	0.4317	Dominant	1.395	0.99-1.967	0.05706	1.066
						Recessive	1.008	0.6833-1.487	0.9679	
						Additive	1.152	0.9256-1.434	0.2048	
						Allelic			0.3019	
rs2853676	5	1288547	T	0.2845	0.2763	Dominant	0.9819	0.7169-1.345	0.9092	0.1079
						Recessive	1.292	0.7517-2.222	0.3535	
						Additive	1.04	0.8165-1.324	0.7516	
						Allelic			0.7426	
rs6869535	5	40597618	A	0.1667	0.1632	Dominant	0.9696	0.6894-1.364	0.8591	
						Recessive	1.495	0.5472-4.086	0.4328	

						Additive	1.011	0.7462-1.37	0.9438	
						Allelic			0.8664	0.02829
rs10079250	5	149450132	C	0.06042	0.06394	Dominant	0.9751	0.6051-1.571	0.9175	
						Recessive	1.061e-009	0-inf	0.9993	
						Additive	0.9558	0.5977-1.529	0.8503	
						Allelic			0.7951	0.06744
rs2252586	7	54978924	T	0.2562	0.2901	Dominant	0.7588	0.5537-1.04	0.08594	
						Recessive	1.106	0.6142-1.991	0.7375	
						Additive	0.8544	0.6639-1.1	0.2214	
						Allelic			0.178	1.815
rs6969537	7	55082418	A	0.1402	0.1224	Dominant	1.239	0.863-1.778	0.2457	
						Recessive	0.6967	0.1371-3.541	0.6631	
						Additive	1.184	0.8456-1.657	0.3259	
						Allelic			0.3426	0.9005
rs11979158	7	55159349	G	0.1757	0.1576	Dominant	1.16	0.8276-1.626	0.3889	
						Recessive	1.291	0.4567-3.648	0.6303	
						Additive	1.151	0.8507-1.556	0.3625	
						Allelic			0.381	0.7676
rs10488631	7	128594183	C	0.1125	0.1174	Dominant	0.9275	0.6301-1.365	0.7028	
						Recessive	0.7406	0.2226-2.464	0.6245	
						Additive	0.9194	0.6529-1.295	0.6305	
						Allelic			0.7843	0.07492

rs12531711	7	128617466	G	0.1176	0.117	Dominant	0.9908	0.6659-1.474	0.9636	0.00121
						Recessive	0.7565	0.2272-2.518	0.6492	
						Additive	0.9689	0.6834-1.374	0.8591	
						Allelic			0.9722	
rs10464870	8	130477823	C	0.2531	0.2284	Dominant	1.163	0.8463-1.598	0.3522	1.079
						Recessive	1.153	0.6177-2.154	0.6541	
						Additive	1.126	0.875-1.449	0.3563	
						Allelic			0.2989	
rs891835	8	130491752	G	0.2668	0.2384	Dominant	1.124	0.8186-1.543	0.4704	1.372
						Recessive	1.428	0.7914-2.577	0.2368	
						Additive	1.143	0.8918-1.466	0.2907	
						Allelic			0.2415	
rs6470745	8	130641921	G	0.2045	0.2019	Dominant	1.131	0.8196-1.561	0.4537	0.01409
						Recessive	0.5598	0.2359-1.329	0.1883	
						Additive	1.022	0.7792-1.342	0.8726	
						Allelic			0.9055	
rs9656979	8	130664407	C	0.4463	0.429	Dominant	0.9949	0.7121-1.39	0.9761	0.3899
						Recessive	1.253	0.8483-1.851	0.2572	
						Additive	1.072	0.8587-1.338	0.5395	
						Allelic			0.5324	
rs16904140	8	130665643	A	0.2234	0.2204	Dominant	1.07	0.7799-1.469	0.6734	
						Recessive	0.8109	0.3921-1.677	0.5716	
						Additive	1.018	0.7841-1.323	0.8914	

						Allelic			0.897	0.01675
rs4295627	8	130685457	G	0.175	0.1867	Dominant	1.007	0.7228-1.404	0.9661	
						Recessive	0.3676	0.1239-1.091	0.07126	
						Additive	0.9176	0.6882-1.223	0.5577	
						Allelic			0.5886	0.2925
rs11823971	11	72388561	A	0.09426	0.09129	Dominant	1.085	0.7221-1.629	0.6952	
						Recessive	0.6434	0.1306-3.17	0.5878	
						Additive	1.041	0.7195-1.507	0.8299	
						Allelic			0.8532	0.03425
rs498872	11	118477367	A	0.2875	0.3126	Dominant	0.8322	0.6085-1.138	0.25	
						Recessive	0.9407	0.5489-1.612	0.824	
						Additive	0.8866	0.6965-1.128	0.328	
						Allelic			0.3293	0.9515
rs17748	11	118528424	T	0.2045	0.2322	Dominant	0.8394	0.6089-1.157	0.2852	
						Recessive	0.6521	0.2997-1.419	0.281	
						Additive	0.8374	0.6391-1.097	0.1979	
						Allelic			0.2333	1.42
rs6089953	20	62291008	A	0.2049	0.249	Dominant	0.7755	0.5631-1.068	0.1195	
						Recessive	0.6218	0.3087-1.252	0.1835	
						Additive	0.7885	0.6069-1.024	0.07524	
						Allelic			0.06119	3.505
rs6010620	20	62309839	A	0.2104	0.2505	Dominant	0.7913	0.5734-1.092	0.1546	

						Recessive	0.6774	0.3429-1.338	0.2622	
						Additive	0.8092	0.623-1.051	0.1125	
						Allelic			0.09215	2.836
rs2297440	20	62312299	T	0.1903	0.242	Dominant	0.7335	0.5225-1.03	0.07344	
						Recessive	0.589	0.2828-1.227	0.1573	
						Additive	0.7555	0.5733-0.9957	0.04654	
						Allelic			0.03246	4.574
rs4809324	20	62318220	C	0.1379	0.1034	Dominant	1.401	0.9676-2.029	0.07416	
						Recessive	2.021	0.5735-7.121	0.2737	
						Additive	1.386	0.991-1.937	0.05651	
						Allelic			0.05273	3.752

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Ψ: MAF=Minor Allele Frequency

£: OR adjusted for age, sex, and country

**Table S2. Summary results for SNPs unassociated with astrocytoma subtype**

SNP	Chr.	Location (bp)	Minor allele	MAF <sup>ψ</sup> in cases	MAF <sup>ψ</sup> in controls	Model	OR <sup>ε</sup>	95% CI	P	CHISQ
rs7530361	1	100462860	C	0.1477	0.1656	Dominant	0.8099	0.5246-1.25	0.3413	0.4891
						Recessive	1.196	0.3775-3.788	0.7612	
						Additive	0.8653	0.5905-1.268	0.4582	
						Allelic			0.4843	
rs501700	1	100520311	A	0.1513	0.1607	Dominant	0.8714	0.5523-1.375	0.5542	0.1259
						Recessive	1.26	0.3966-4.001	0.6953	
						Additive	0.9245	0.6225-1.373	0.6973	
						Allelic			0.7228	
rs2072532	2	40366301	G	0.4773	0.4317	Dominant	1.316	0.8606-2.013	0.205	1.739
						Recessive	1.214	0.7672-1.919	0.4082	
						Additive	1.19	0.9125-1.551	0.1993	
						Allelic			0.1873	
rs2736100	5	1286516	A	0.4924	0.4958	Dominant	0.7539	0.4876-1.165	0.2037	0.009789
						Recessive	1.298	0.8349-2.019	0.2466	
						Additive	0.9888	0.7476-1.308	0.9369	
						Allelic			0.9212	
rs2853676	5	1288547	T	0.303	0.2763	Dominant	1.047	0.7102-1.544	0.8161	

						Recessive	1.588	0.8522-2.959	0.1453	
						Additive	1.131	0.843-1.518	0.4115	
						Allelic			0.3924	0.7314
rs6869535	5	40597618	A	0.1641	0.1632	Dominant	0.9237	0.6021-1.417	0.7161	
						Recessive	2.072	0.6797-6.317	0.2002	
						Additive	1.011	0.6934-1.475	0.9536	
						Allelic			0.9708	0.001336
rs10079250	5	149450132	C	0.04924	0.06394	Dominant	0.7689	0.407-1.453	0.4182	
						Recessive	2.186e-009	0-inf	0.9993	
						Additive	0.7602	0.406-1.423	0.3916	
						Allelic			0.3763	0.7829
rs2252586	7	54978924	T	0.2652	0.2901	Dominant	0.7586	0.5136-1.12	0.1649	
						Recessive	1.277	0.6409-2.546	0.4866	
						Additive	0.8796	0.6438-1.202	0.4202	
						Allelic			0.4272	0.6304
rs6969537	7	55082418	A	0.1346	0.1224	Dominant	1.129	0.7183-1.773	0.5996	
						Recessive	1.205	0.2371-6.125	0.8221	
						Additive	1.12	0.7413-1.691	0.5913	
						Allelic			0.5967	0.2801
rs11979158	7	55159349	G	0.2061	0.1576	Dominant	1.49	0.9933-2.235	0.05391	
						Recessive	1.541	0.4693-5.061	0.4759	
						Additive	1.424	0.9948-2.038	0.05341	
						Allelic			0.06275	3.463



rs10488631	7	128594183	C	0.1174	0.1174	Dominant	1.027	0.6402-1.648	0.912	1.133e-006
						Recessive	0.7715	0.1624-3.664	0.7441	
						Additive	1.001	0.6571-1.524	0.9976	
						Allelic			0.9992	
rs12531711	7	128617466	G	0.1293	0.117	Dominant	1.171	0.7184-1.908	0.527	0.2661
						Recessive	0.8077	0.1698-3.843	0.7884	
						Additive	1.11	0.7224-1.705	0.6342	
						Allelic			0.606	
rs10464870	8	130477823	C	0.1962	0.2284	Dominant	0.8254	0.5495-1.24	0.3552	1.233
						Recessive	0.6168	0.2334-1.63	0.3299	
						Additive	0.8234	0.5873-1.154	0.2597	
						Allelic			0.2669	
rs891835	8	130491752	G	0.2093	0.2384	Dominant	0.8313	0.5557-1.244	0.3685	0.963
						Recessive	0.7296	0.2952-1.803	0.4946	
						Additive	0.8448	0.6059-1.178	0.3201	
						Allelic			0.3264	
rs6470745	8	130641921	G	0.1641	0.2019	Dominant	0.8657	0.5726-1.309	0.4941	1.877
						Recessive	0.1466	0.0196-1.097	0.06147	
						Additive	0.7826	0.5451-1.123	0.1839	
						Allelic			0.1707	
rs9656979	8	130664407	C	0.416	0.429	Dominant	0.9272	0.6145-1.399	0.7186	
						Recessive	0.9248	0.5521-1.549	0.7663	

						Additive	0.9433	0.7124-1.249	0.6839	
						Allelic			0.7064	0.1419
rs16904140	8	130665643	A	0.1917	0.2204	Dominant	0.8733	0.5848-1.304	0.5081	
						Recessive	0.5263	0.1801-1.538	0.2407	
						Additive	0.843	0.6008-1.183	0.3231	
						Allelic			0.3135	1.016
rs4295627	8	130685457	G	0.1477	0.1867	Dominant	0.8255	0.5404-1.261	0.3751	
						Recessive	0.1668	0.02217-1.255	0.08194	
						Additive	0.7625	0.5244-1.109	0.1558	
						Allelic			0.1433	2.143
rs11823971	11	72388561	A	0.08271	0.09129	Dominant	0.879	0.5153-1.499	0.6358	
						Recessive	1.112	0.2245-5.512	0.8962	
						Additive	0.9115	0.5677-1.464	0.7014	
						Allelic			0.6642	0.1884
rs498872	11	118477367	A	0.2885	0.3126	Dominant	0.8131	0.5509-1.2	0.2975	
						Recessive	1.021	0.5314-1.96	0.9513	
						Additive	0.8895	0.659-1.201	0.4444	
						Allelic			0.4542	0.5601
rs17748	11	118528424	T	0.2099	0.2322	Dominant	0.916	0.6152-1.364	0.6655	
						Recessive	0.5087	0.1739-1.489	0.2173	
						Additive	0.8681	0.6205-1.214	0.4089	
						Allelic			0.4456	0.5817

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**Ψ**: MAF=Minor Allele Frequency      **£**: OR adjusted for age, sex, and country

**Table S3. Summary results for SNPs unassociated with non-astrocytoma subtypes**

SNP	Chr.	Location (bp)	Minor allele	MAF <sup>ψ</sup> in cases	MAF <sup>ψ</sup> in controls	Model	OR <sup>‡</sup>	95% CI	P	CHISQ
rs7530361	1	100462860	C	0.1396	0.1656	Dominant	0.8026	0.5004-1.287	0.3617	0.9025
						Recessive	0.7271	0.1586-3.333	0.6816	
						Additive	0.817	0.5339-1.25	0.3517	
						Allelic			0.3421	
rs501700	1	100520311	A	0.1442	0.1607	Dominant	0.866	0.5328-1.408	0.5617	0.3455
						Recessive	0.7255	0.1583-3.326	0.6796	
						Additive	0.869	0.5639-1.339	0.5243	
						Allelic			0.5567	
rs2072532	2	40366301	G	0.4398	0.4317	Dominant	1.508	0.941-2.416	0.08778	0.04695
						Recessive	0.7903	0.4447-1.405	0.4225	
						Additive	1.115	0.8256-1.505	0.4783	
						Allelic			0.8285	
rs2853676	5	1288547	T	0.2617	0.2763	Dominant	0.9002	0.5865-1.382	0.6307	0.1868
						Recessive	0.9824	0.4376-2.206	0.9657	
						Additive	0.9332	0.6636-1.312	0.6908	
						Allelic			0.6656	
rs6869535	5	40597618	A	0.1697	0.1632	Dominant	1.012	0.6412-1.598	0.9584	

						Recessive	0.8717	0.1822-4.17	0.8635	
						Additive	1	0.6607-1.514	0.9999	
						Allelic			0.814	0.05535
rs10079250	5	149450132	C	0.07407	0.06394	Dominant	1.257	0.6855-2.303	0.4602	
						Recessive	2.145e-009	0-inf	0.9993	
						Additive	1.218	0.6728-2.204	0.5152	
						Allelic			0.5876	0.2941
rs2252586	7	54978924	T	0.2454	0.2901	Dominant	0.77	0.5012-1.183	0.233	
						Recessive	0.8852	0.3769-2.079	0.7795	
						Additive	0.8259	0.5816-1.173	0.2849	
						Allelic			0.1874	1.738
rs6969537	7	55082418	A	0.1468	0.1224	Dominant	1.389	0.8617-2.24	0.1774	
						Recessive	2.685e-009	0-inf	0.9984	
						Additive	1.257	0.8045-1.965	0.3149	
						Allelic			0.3286	0.9543
rs11979158	7	55159349	G	0.1389	0.1576	Dominant	0.8264	0.5105-1.338	0.438	
						Recessive	0.8848	0.1845-4.242	0.8784	
						Additive	0.8477	0.5475-1.312	0.4586	
						Allelic			0.4925	0.471
rs10488631	7	128594183	C	0.1065	0.1174	Dominant	0.8154	0.4766-1.395	0.4564	
						Recessive	0.6751	0.1403-3.248	0.624	
						Additive	0.8262	0.5169-1.321	0.4251	
						Allelic			0.6501	0.2057

rs12531711	7	128617466	G	0.1048	0.117	Dominant	0.8133	0.4701-1.407	0.4601	0.2514
						Recessive	0.6777	0.141-3.257	0.6271	
						Additive	0.8255	0.5128-1.329	0.4299	
						Allelic			0.6161	
rs6470745	8	130641921	G	0.2523	0.2019	Dominant	1.543	1.009-2.36	0.04533	2.742
						Recessive	1.061	0.4152-2.709	0.9022	
						Additive	1.341	0.9536-1.886	0.09157	
						Allelic			0.09774	
rs9656979	8	130664407	C	0.482	0.429	Dominant	1.101	0.6968-1.741	0.6794	2.053
						Recessive	1.755	1.071-2.877	0.02563	
						Additive	1.264	0.9367-1.705	0.1255	
						Allelic			0.1519	
rs16904140	8	130665643	A	0.2613	0.2204	Dominant	1.365	0.8956-2.081	0.1477	1.713
						Recessive	1.182	0.4929-2.836	0.7075	
						Additive	1.256	0.8964-1.759	0.1856	
						Allelic			0.1906	
rs4295627	8	130685457	G	0.2083	0.1867	Dominant	1.288	0.8312-1.996	0.2574	0.533
						Recessive	0.6115	0.1763-2.121	0.4383	
						Additive	1.136	0.7867-1.639	0.4974	
						Allelic			0.4654	
rs1063192	9	22003367	G	0.5229	0.4506	Dominant	1.253	0.7802-2.012	0.3508	
						Recessive	1.594	0.9966-2.55	0.05169	

						Additive	1.288	0.9646-1.72	0.08627	
						Allelic			0.05402	3.712
rs2157719	9	22033366	C	0.5093	0.4383	Dominant	1.324	0.8259-2.122	0.2438	
						Recessive	1.527	0.9445-2.468	0.0842	
						Additive	1.292	0.9665-1.728	0.08364	
						Allelic			0.05833	3.584
rs1412829	9	22043926	G	0.5	0.4338	Dominant	1.253	0.7896-1.989	0.3382	
						Recessive	1.532	0.9485-2.474	0.08117	
						Additive	1.267	0.9494-1.691	0.108	
						Allelic			0.07408	3.19
rs4977756	9	22068652	G	0.4673	0.4224	Dominant	1.11	0.7018-1.756	0.6556	
						Recessive	1.4	0.844-2.324	0.1924	
						Additive	1.167	0.8676-1.571	0.3069	
						Allelic			0.231	1.434
rs11823971	11	72388561	A	0.1081	0.09129	Dominant	1.419	0.8441-2.385	0.1867	
						Recessive	3.647e-009	0-inf	0.9983	
						Additive	1.269	0.7834-2.054	0.3334	
						Allelic			0.4397	0.5971
rs498872	11	118477367	A	0.2864	0.3126	Dominant	0.8545	0.5609-1.302	0.4641	
						Recessive	0.8299	0.3899-1.766	0.6285	
						Additive	0.8778	0.6322-1.219	0.4365	
						Allelic			0.4469	0.5786

rs17748	11	118528424	T	0.1982	0.2322	Dominant	0.767	0.4953-1.188	0.2344	1.193
						Recessive	0.8286	0.3069-2.237	0.7105	
						Additive	0.8104	0.561-1.171	0.2625	
						Allelic			0.2748	
rs6089953	20	62291008	A	0.2342	0.249	Dominant	0.9747	0.6365-1.493	0.906	0.2109
						Recessive	0.7992	0.3233-1.976	0.6275	
						Additive	0.9504	0.6737-1.341	0.7721	
						Allelic			0.6461	
rs6010620	20	62309839	A	0.2361	0.2505	Dominant	0.9816	0.6375-1.511	0.9329	0.1962
						Recessive	0.8028	0.3236-1.992	0.6356	
						Additive	0.9552	0.6749-1.352	0.796	
						Allelic			0.6578	
rs2297440	20	62312299	T	0.2108	0.242	Dominant	0.8803	0.56-1.384	0.5805	0.8917
						Recessive	0.6877	0.258-1.833	0.454	
						Additive	0.8708	0.6042-1.255	0.458	
						Allelic			0.345	
rs4809324	20	62318220	C	0.1216	0.1034	Dominant	1.203	0.726-1.994	0.4729	0.6276
						Recessive	0.7842	0.08663-7.099	0.8288	
						Additive	1.158	0.7253-1.849	0.539	
						Allelic			0.4282	

Ψ: MAF=Minor Allele Frequency

£: OR adjusted for age, sex, and country



**Table S4. Number of subjects for each genotype of SNPs associated with pediatric brain tumors**

SNP	Gene	Genotype	Cases	Controls
All brain tumors				
rs2736100	TERT	CC	76	113
		CA	103	256
		AA	61	109
rs1063192	CDKN2BAS CDKN2B	AA	56	150
		AG	116	212
		GG	67	104
rs2157719	CDKN2BAS	TT	58	159
		TC	117	219
		CC	63	100
rs1412829	CDKN2BAS	AA	62	159
		AG	118	221
		GG	63	96
rs4977756	CDKN2BAS	AA	62	164
		AG	121	223
		GG	55	90
Astrocytoma				
rs1063192	CDKN2BAS CDKN2B	AA	27	150
		AG	70	212
		GG	33	104
rs2157719	CDKN2BAS	TT	29	159
		TC	69	219
		CC	32	100
rs1412829	CDKN2BAS	AA	31	159
		AG	69	221
		GG	32	69
rs4977756	CDKN2BAS	AA	29	164
		AG	73	223
		GG	29	90
rs6089953	RTEL1	GG	90	277
		GA	38	170
		AA	5	35
rs6010620	RTEL1	GG	88	272
		GA	38	168
		AA	6	35
rs2297440	RTEL1	CC	86	258
		CT	33	145

rs4809324	RTEL1	TT	5	33
		TT	96	381
		TC	32	88
		CC	4	5
<hr/>				
Other				
rs2736100	TERT	CC	38	113
		CA	46	256
		AA	25	109
rs10464870	CCDC26	TT	52	287
		TC	47	159
		CC	12	29
rs891835	CCDC26	TT	51	277
		TG	43	168
		GG	15	29

**Table S5. Summary results for SNPs associated with pediatric brain tumors in Denmark**

SNP	Chr.	Gene	Location (bp)	Minor allele	MAF <sup>a</sup> in cases	MAF <sup>a</sup> in controls	Model	OR <sup>b</sup>	95% CI	P	CHISQ
rs2736100	5	<i>TERT</i>	1286516	A	0.47	0.48	Dominant	0.76	0.38-1.50	0.427	
							Recessive	1.18	0.58-2.41	0.647	
							Additive	0.95	0.62-1.47	0.826	
							Allelic			0.864	
rs1063192	9	<i>CDKN2BAS</i> <i>CDKN2B</i>	22003367	G	0.54	0.49	Dominant	1.12	0.56-2.26	0.751	0.03
							Recessive	1.56	0.76-3.21	0.227	
							Additive	1.21	0.80-1.82	0.362	
							Allelic			0.33	
rs2157719	9	<i>CDKN2BAS</i>	22033366	C	0.54	0.46	Dominant	1.78	0.85-3.73	0.125	
							Recessive	1.27	0.63-2.56	0.496	
							Additive	1.34	0.87-2.05	0.179	
							Allelic			0.159	
rs1412829	9	<i>CDKN2BAS</i>	22043926	G	0.52	0.46	Dominant	1.45	0.73-2.91	0.283	1.96
							Recessive	1.19	0.60-2.38	0.611	
							Additive	1.23	0.81-1.85	0.336	
							Allelic			0.315	
rs4977756	9	<i>CDKN2BAS</i>	22068652	G	0.48	0.43	Dominant	1.61	0.81-3.19	0.174	1.01
							Recessive	1.04	0.49-2.20	0.909	
							Additive	1.23	0.80-1.88	0.343	
							Allelic			0.337	

**a:** MAF=Minor Allele Frequency

**b:** OR adjusted for age, and sex

**Table S6. Summary results for SNPs associated with pediatric brain tumors in Norway**

SNP	Chr.	Gene	Location (bp)	Minor allele	MAF <sup>a</sup> in cases	MAF <sup>a</sup> in controls	Model	OR <sup>b</sup>	95% CI	P	CHISQ
rs2736100	5	<i>TERT</i>	1286516	A	0.42	0.58	Dominant	0.42	0.12-1.41	0.161	
							Recessive	0.39	0.13-1.17	0.093	
							Additive	0.50	0.24-1.03	0.059	
							Allelic			0.052	
rs1063192	9	<i>CDKN2BAS</i> <i>CDKN2B</i>	22003367	G	0.48	0.43	Dominant	2.06	0.67-6.34	0.206	3.78
							Recessive	1.02	0.31-3.31	0.979	
							Additive	1.33	0.68-2.61	0.407	
							Allelic			0.545	
rs2157719	9	<i>CDKN2BAS</i>	22033366	C	0.50	0.40	Dominant	2.19	0.73-6.56	0.161	0.37
							Recessive	1.49	0.47-4.73	0.493	
							Additive	1.57	0.79-3.08	0.193	
							Allelic			0.244	
rs1412829	9	<i>CDKN2BAS</i>	22043926	G	0.48	0.39	Dominant	2.29	0.77-6.83	0.138	1.36
							Recessive	1.19	0.36-3.97	0.774	
							Additive	1.49	0.76-2.94	0.248	
							Allelic			0.317	
rs4977756	9	<i>CDKN2BAS</i>	22068652	G	0.44	0.40	Dominant	1.70	0.59-4.91	0.326	1.00
							Recessive	0.83	0.24-2.93	0.774	
							Additive	1.18	0.61-2.31	0.620	
							Allelic			0.710	

**a:** MAF=Minor Allele Frequency

**b:** OR adjusted for age, and sex

**Table S7. Summary results for SNPs associated with pediatric brain tumors in Sweden**

SNP	Chr.	Gene	Location (bp)	Minor allele	MAF <sup>a</sup> in cases	MAF <sup>a</sup> in controls	Model	OR <sup>b</sup>	95% CI	P	CHISQ
rs2736100	5	<i>TERT</i>	1286516	A	0.48	0.50	Dominant	0.58	0.33-1.01	0.055	
							Recessive	1.44	0.81-2.55	0.216	
							Additive	0.92	0.65-1.31	0.651	
							Allelic			0.587	
rs1063192	9	<i>CDKN2BAS</i> <i>CDKN2B</i>	22003367	G	0.57	0.46	Dominant	1.77	1.02-3.09	0.044	0.29
							Recessive	1.76	0.97-3.18	0.061	
							Additive	1.53	1.08-2.18	0.018	
							Allelic			0.016	
rs2157719	9	<i>CDKN2BAS</i>	22033366	C	0.54	0.45	Dominant	1.64	0.93-2.88	0.089	5.75
							Recessive	1.68	0.96-2.94	0.068	
							Additive	1.45	1.03-2.05	0.032	
							Allelic			0.029	
rs1412829	9	<i>CDKN2BAS</i>	22043926	G	0.54	0.44	Dominant	1.57	0.89-2.75	0.113	4.73
							Recessive	1.85	1.06-3.25	0.031	
							Additive	1.49	1.05-2.09	0.024	
							Allelic			0.021	
rs4977756	9	<i>CDKN2BAS</i>	22068652	G	0.53	0.44	Dominant	1.57	0.89-2.77	0.122	5.34
							Recessive	1.72	0.96-3.08	0.067	
							Additive	1.45	1.02-2.07	0.039	
							Allelic			0.039	

**a:** MAF=Minor Allele Frequency      **b:** OR adjusted for age, and sex